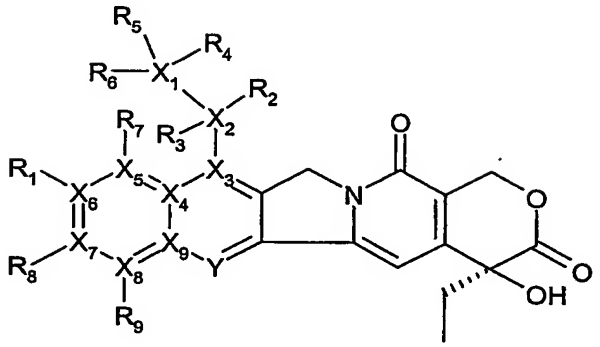
CLAIMS

1. A stable labeled camptothecin analogs of formula (I)



(I)

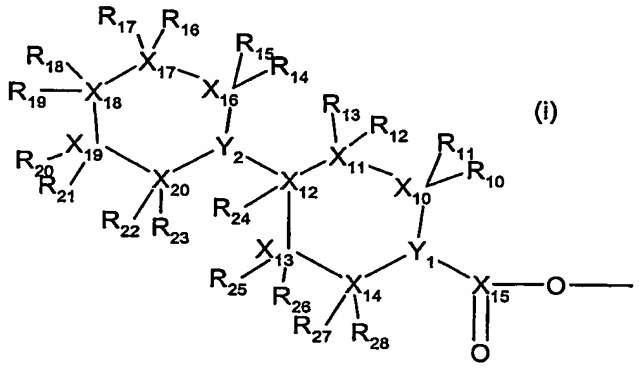
wherein

each of R_2, R_3, R_4, R_5, R_6, R_7, R_8 and R_9 independentently represents ^2H or H;

each of X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8 and X_9 independently represents ^{13}C or C;

Y is ^{15}N or N; and

R_1 is a hydroxyl group or a group of formula (i)



(i)

wherein

each of R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{23}, R_{24}, R_{25}, R_{26}, R_{27} and R_{28} independently represents ^{2}H or H,
each of X_{10}, X_{11}, X_{12}, X_{13}, X_{14}, X_{15}, X_{16}, X_{17}, X_{18}, X_{19} and X_{20} independently represents ^{13}C or C,
each of Y_1 and Y_2 independently represents ^{15}N or N;
with the proviso that at least one of R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{23}, R_{24}, R_{25}, R_{26}, R_{27}, R_{28}, X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8, X_9, X_{10}, X_{11}, X_{12}, X_{13}, X_{14}, X_{15}, X_{16}, X_{17}, X_{18}, X_{19}, X_{20}, Y, Y_1 and Y_2 is isotopically labeled;
or a pharmaceutically acceptable salt thereof.

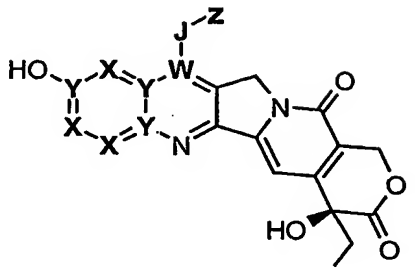
2. A compound of formula (I) as claimed in claim 1, wherein R_1 is a hydroxyl group.

3. A compound of formula (I) as claimed in claim 1, wherein R_1 is a group of formula (i) as defined in claim 1.

4. A compound of formula (I) as claimed in claim 1, wherein R_2, R_3, R_4, R_5, R_6, R_7, R_8 and R_9 are all H, X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8 and X_9 are all C, Y is N and R_1 is a group (i) as defined in claim 1.

5. A compound of formula (I) as claimed in claim 1, wherein each of R_2, R_3, R_4, R_5, R_6, R_7, R_8 and R_9 independently represents ^{2}H of H, each of X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8 and X_9 independently represents ^{13}C or C, Y is ^{15}N or N, R_1 is a hydroxyl group or a group of formula (i) wherein R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{23}, R_{24}, R_{25}, R_{26}, R_{27} and R_{28} are all H, X_{10}, X_{11}, X_{12}, X_{13}, X_{14}, X_{15}, X_{16}, X_{17}, X_{18}, X_{19} and X_{20} are all C and Y_1 and Y_2 are N.

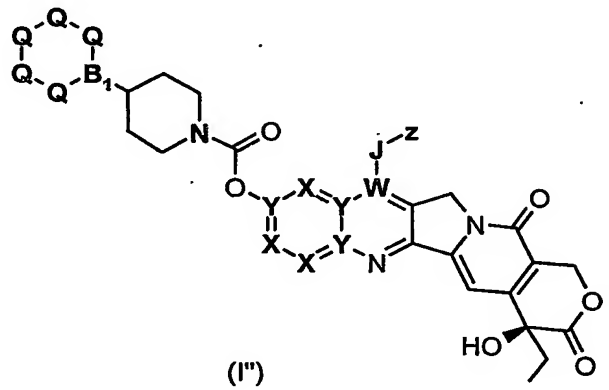
6. A compound of formula (I')



(I')

as defined in TABLE 1.

7. A compound of formula (I"), optionally in the form of a pharmaceutical acceptable salt,



(I")

as defined in TABLE 2.

8. A process for the preparation of a stable labeled camptothecin analog of formula (I) as defined in claim 1, wherein

R_1 is a hydroxyl group,

each of R_2, R_3, R_4, R_5, R_6, R_7, R_8 and R_9 independently represents ^2H or H,

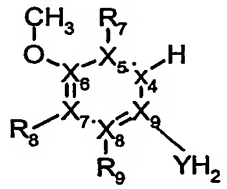
each of X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8 and X_9 independently represents ^{13}C or C, and

Y is ^{15}N or N,

with the proviso that at least one of R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8, X_9 and Y is isotopically labeled,

which comprises:

(a) reacting a compound of formula (II)



(II)

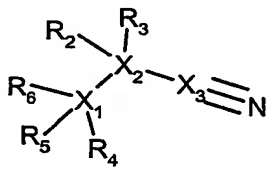
wherein

each of R_7, R_8 and R_9 independently represents ^2H or H,

each of X_4, X_5, X_6, X_7, X_8 and X_9 independently represents ^{13}C or C, and

Y is ^{15}N or N,

with a compound of formula (III)



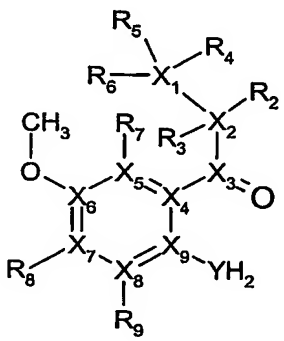
(III)

wherein

each of R_2, R_3, R_4, R_5 and R_6 independently represents ^2H or H, and

each of X_1, X_2 and X_3 independently represents ^{13}C or C,

to obtain the compound of formula (IV)



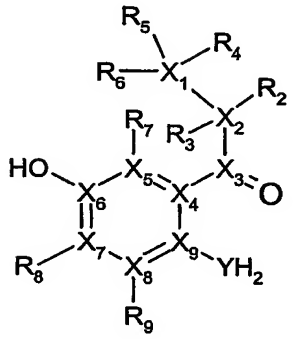
(IV)

wherein

each of R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8, X_9 and Y, are as above described,

so that at least one of R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8, X_9 and Y is isotopically labeled;

(b) cleaving a compound of formula (IV) to obtain a compound of formula (V)

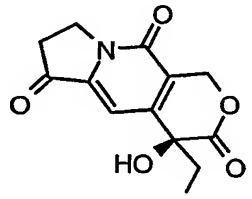


(V)

wherein

R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8, X_9 and Y are as above described for the compound (IV); and

(c) reacting a compound of formula (V) with the compound of formula (VI)



(VI)

to obtain the desired compound of formula (I).

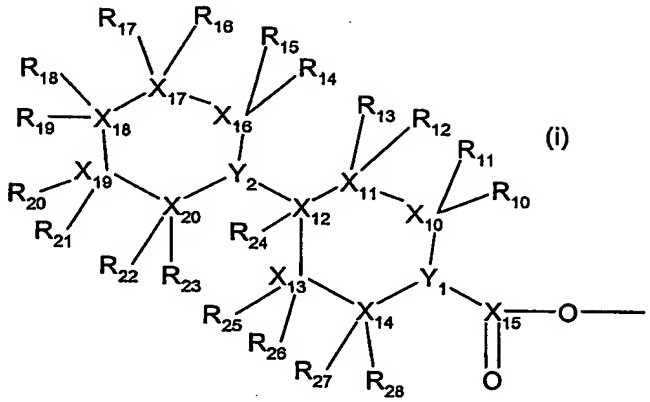
9. A process for preparing a compound of formula (I) as defined in claim 1, wherein

each of R_2, R_3, R_4, R_5, R_6, R_7, R_8 and R_9 independently represents ^2H or H,

each of X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8 and X_9 independently represents ^{13}C or C,

Y is ^{15}N or N, and

R_1 is a group of formula (i)



wherein

each of R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{23}, R_{24}, R_{25}, R_{26}, R_{27} and R_{28} independently represents ^2H or H,

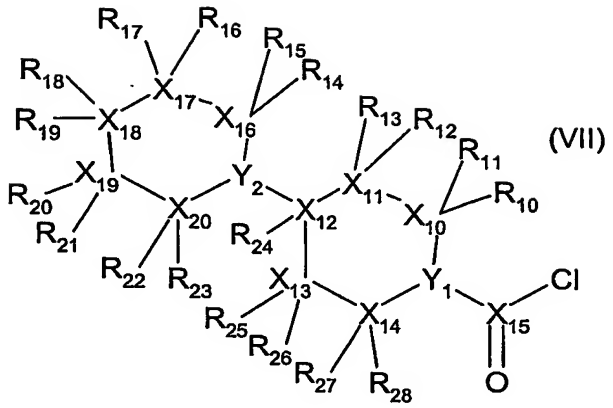
each of X_{10}, X_{11}, X_{12}, X_{13}, X_{14}, X_{15}, X_{16}, X_{17}, X_{18}, X_{19} and X_{20} independently represents ^{13}C or C, and

each of Y_1 and Y_2 independently represents ^{15}N or N,

with the proviso that at least one of R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8, X_9 and Y is isotopically labeled, and that at least one of R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{23}, R_{24}, R_{25}, R_{26}, R_{27}, R_{28}, X_{10}, X_{11}, X_{12}, X_{13}, X_{14}, X_{15}, X_{16}, X_{17}, X_{18}, X_{19}, X_{20}, Y_1 and Y_2 is isotopically labeled,

which comprises:

(d) reacting a compound of formula (I) as obtaned in step (c) above with a compound of formula (VII)



wherein

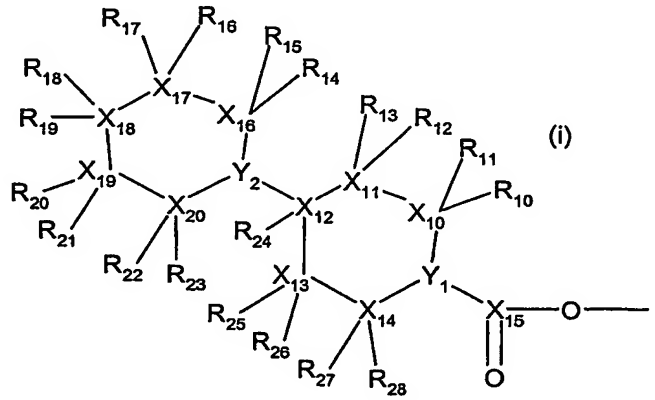
each of R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{23}, R_{24}, R_{25}, R_{26}, R_{27} and R_{28} independentently represents ^{2}H or H,

each of X_{10}, X_{11}, X_{12}, X_{13}, X_{14}, X_{15}, X_{16}, X_{17}, X_{18} and X_{20} independently represents ^{13}C or C, and

each of Y_1 and Y_2 independently represents ^{15}N or N,

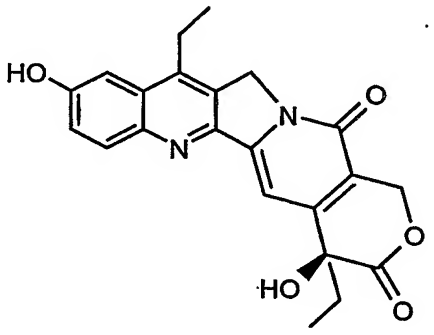
with the proviso that at least one of R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{23}, R_{24}, R_{25}, R_{26}, R_{27}, R_{28}, X_{10}, X_{11}, X_{12}, X_{13}, X_{14}, X_{15}, X_{16}, X_{17}, X_{18}, X_{19}, X_{20}, Y_1 and Y_2 is isotopically labeled, to obtain the desired compound of formula (I).

10. A process for preparing a compound of formula (I) as defined in claim 1, wherein R_2, R_3, R_4, R_5, R_6, R_7, R_8 and R_9 are all H; X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8, and X_9 are all C, Y is N and R_1 is a group of formula (i)



wherein
each of R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{23}, R_{24}, R_{25}, R_{26}, R_{27} and R_{28} independently represents ^{2}H or H,
each of X_{10}, X_{11}, X_{12}, X_{13}, X_{14}, X_{15}, X_{16}, X_{17}, X_{18}, X_{19} and X_{20} independently represents ^{13}C or C, and
each of Y_1 and Y_2 independently represents ^{15}N or N,
with the proviso that at least one of R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{23}, R_{24}, R_{25}, R_{26}, R_{27}, R_{28}, X_{10}, X_{11}, X_{12}, X_{13}, X_{14}, X_{15}, X_{16}, X_{17}, X_{18}, X_{19}, X_{20}, Y_1 and Y_2 is isotopically labeled,
which comprises:

(e) reacting the compound of formula



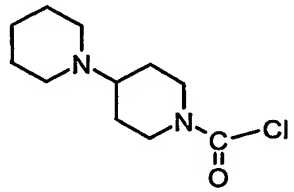
(SN-38)

with a compound of formula (VII) as above described to obtain the desired compound of formula (I), and optionally converting it into a pharmaceutically acceptable salt thereof.

11. A process for preparing a compound of formula (I) as defined in claim 1, wherein
each of R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8, X_9 and Y, are as above described, with the proviso that at least one of R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8, X_9 and Y is isotopically labeled, and

R_1 is a group of formula (i) wherein R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{23}, R_{24}, R_{25}, R_{26}, R_{27}, R_{28} are all H and X_{10}, X_{11}, X_{12}, X_{13}, X_{14}, X_{15}, X_{16}, X_{17}, X_{18}, X_{19} and X_{20} are all C, Y_1 and Y_2 are N, which comprises:

(f) reacting a compound of formula (I) as obtained in step (c) above with the compound of formula



to obtain the desired compound of formula (I), and optionally converting it into a pharmaceutically acceptable salt thereof.

12. Use of a stable labeled camptothecin analog of formula (I) as claimed in claim 1, for ADME studies.

13. Use of a stable labeled camptothecin analog of formula (I) as claimed in claim 1, as an internal standard in an analytical method for the quantitative detection of the corresponding unlabeled camptothecin analog in a biological sample.

14. Use of a stable labeled camptothecin analog of formula (I') as claimed in claim 6 and formula (I") as claimed in claim 7 or a pharmaceutically acceptable salt thereof as an internal standard in an analytical method for the quantitative detection of the corresponding unlabeled camptothecin analog in a biological sample.